Complete Summary

GUIDELINE TITLE

The management of thymoma: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Falkson C, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak D, Yu E, Smith CA, McNair S, Ung Y, Evans WK, Lung Disease Site Group. The management of thymoma: guideline recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2008 Sep 26. 41 p. (Evidence-based series; no. 7-11). [58 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Stage I thymoma
- Stage II thymoma
- Stage III thymoma
- Stage IVa thymoma

- Stage IVb thymoma
- Locally advanced thymoma
- Unresectable thymoma
- Recurrent thymoma

Note: This guideline excludes thymic carcinoma and carcinoid tumors.

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Endocrinology
Oncology
Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the optimal management of thymoma
- To promote evidence-based practice in Ontario, Canada

TARGET POPULATION

Adult patients with thymoma (excluding thymic carcinoma and carcinoids)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Computerized tomography (CT)-guided core-needle biopsy
2. Open surgical biopsy

Treatment

1. Surgery (complete and incomplete resections)
    - Open median sternotomy
    - Minimally invasive approaches, e.g., video-assisted thoracic surgery (VATS) – not recommended
    - Thoracotomy
    - Maximum debulking
2. Chemotherapy
    - Cisplatin-based therapy alone or in combination chemotherapy

    - Octreotide alone or with a corticosteroid
3. Radiotherapy
4. Concurrent chemotherapy plus radiotherapy
5. Surgery plus radiotherapy or chemotherapy
6. Sequencing of multimodality therapy
    - Adjuvant radiotherapy and/or chemotherapy
    - Neoadjuvant radiotherapy and/or chemotherapy

MAJOR OUTCOMES CONSIDERED

- Response rates (complete response, overall response)
- Survival (2 year, 5 year, 10 year, overall, disease-free, progression-free)
- Recurrence rate
- Complete and incomplete resection rate
- Toxicity rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The MEDLINE (Ovid) (1996 through June 2006) database was searched for relevant published systematic reviews and primary studies. Search terms included "thymoma" or "thymic neoplasms." Relevant articles and abstracts were selected and reviewed by a methodologist.

Study Selection Criteria

Studies were included in this systematic review if they were:

1. Primary research studies of any design type (e.g., randomized controlled trial [RCT], prospective study, retrospective chart audit).
2. Prospective reports with greater than 10 patients, or retrospective studies with 100 or more patients.
3. Published in English.
4. Reported data on patients with thymoma.
5. Reported data with both of the following features:
    a. Single or multi-modality treatment strategies involving surgery, chemotherapy, or radiotherapy.
    b. Clinical outcomes for treated patients, including response, survival, and toxicity rates.

Studies were excluded in this systematic review if they were:

1. Studies dealing solely with thymic carcinoids or thymic carcinoma, and trials that pooled survival data of patients with thymoma, thymic carcinoma, or other mediastinal tumours.
2. Studies focusing on myasthenia gravis.
3. Letters, reviews, and editorials reporting trial data.

Trials published in a language other than English.

NUMBER OF SOURCE DOCUMENTS

Thirteen studies: 1 randomized controlled trial (RCT), 3 retrospective case reports 1 survey, and 9 prospective studies of chemotherapy

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Methods

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-based Care (CCO's PEBC) use the methods of the Practice Guidelines Development Cycle 1. The Lung Disease Site Group (DSG) conducted a systematic review of the literature to establish an evidentiary base for the development of clinical practice recommendations for thymoma. Key research questions and clinical outcomes were established *a priori* by a working group of clinicians, and a systematic search strategy was developed and conducted in consultation with a research methodologist. Precise inclusion and exclusion criteria were established, and the retrieved literature was filtered using these criteria. Data were extracted from the selected publications, double checked by a second reviewer for accuracy, and summarized in table format.

Synthesizing the Evidence

The relevant outcome data from the selected studies were tabulated in tables and arranged by study design and modality for analysis. Most of the included studies were retrospective chart audits of patients receiving different treatments for various stages of disease. The few available prospective trials included patients with advanced stage (III/IV) thymoma treated with chemotherapy and/or radiotherapy and used a number of different treatment approaches. Because of this heterogeneity, the data were not appropriate for statistical pooling.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Thymoma Working Group (TWG; the authors of this report) used a modified Delphi approach to develop draft guideline recommendations through consensus. The steps in the process are outlined in Figure 1 in the original guideline document. In the first phase, the TWG drafted and confirmed a preliminary set of thirty-eight recommendations related to key treatment issues in the management of thymoma. In this phase, discussions were conducted through teleconference and email communication and were informed by the evidence presented in the systematic review above, additional evidence provided in narrative reviews of the topic, and the clinical experience of members. The objective of the second phase, Round One Consensus, was to obtain consensus on the draft recommendations by clinicians who treat thymoma. The larger group is referred to as the Consensus Group (CG; Figure 1 in the original guideline document). Prior to the first consensus round, a letter was sent to prospective members of the CG requesting their participation in the consensus process. This group consisted of members of the TWG, members of the Program in Evidence-based Care (PEBC) Provincial Lung Disease Site Group (DSG) (n=28), members of the PEBC Hematology DSG for whom this type of practice was thought to be relevant (n=14), and thoracic surgeons (n=27) from across Canada who were identified by the TWG as physicians involved in the management of thymoma. Subsequently, the systematic review, draft recommendations, and questionnaire were mailed to the CG. In the questionnaire, respondents were asked to provide their opinion on general questions about the report and were also asked to rate their agreement with each recommendation on a seven-point Likert scale, ranging from "strongly agree" at 1, through "neither agree or disagree" at 4, to "strongly disagree" at 7.

The first round feedback was analysed and distributed to the TWG, and the members revised the initial recommendations in response. In the second consensus round, a package was again sent to the CG, consisting of the original recommendations, the results of the first consensus round, the modified recommendations in response to the first round feedback, and a questionnaire. For revised recommendations, CG members were asked to rate their preference for both the original Round One recommendation, and a modification to that recommendation. The questionnaire used for Round Two is included as Appendix 1 of the original guideline document. The responses to the second round consultation were analyzed and reviewed by the TWG and final recommendations established. See the original guideline document for additional details.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the publication of this evidence-based series report, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The key issue raised by the Panel was a need to better explain the consensus method. The Panel noted confusion particularly around what is meant by consensus versus agreement. The Lung Disease Site Group (DSG) agreed that the section outlining the consensus process could use clarification and the section was revised. Additional editorial changes suggested by the panel were also made.

Methods

Following the review and discussion of Sections 1 and 2 of this evidence-based series and the review and approval of the report by the PEBC Report Approval Panel and the Thymoma Working Group, the Lung Cancer DSG decided the report was ready for publication. Having engaged all the clinicians who treat thymoma through the consensus process, the DSG felt there was no additional benefit to recirculating the document for further review and feedback.

Conclusion

This evidence-based series (EBS) report reflects the integration of feedback obtained through the external review process with final approval given by the Lung DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Stage I

Surgery

1. Complete surgical resection of the entire thymus gland, including all mediastinal tissues anterior to the pericardium, aorta, and superior vena cava from phrenic nerve to phrenic nerve laterally and from the diaphragm inferiorly to the level of the thyroid gland superiorly, including the upper poles of the thymus, is recommended as the standard of care.
2. For resection of thymoma, an open median sternotomy surgical approach is recommended.

3. Minimally invasive approaches (e.g., video-assisted thoracic surgery [VATS]) are not considered the standard of care and are not recommended at this time.

Radiotherapy

4. Neither postoperative nor neoadjuvant radiotherapy is recommended for stage I disease.

Systemic Therapy

5. Neither postoperative nor neoadjuvant systemic therapy is recommended for stage I disease.

Medically Inoperable Stage I Disease

6. Chemoradiation or radiation alone should be considered for patients who are medically unfit for surgery.

Stage II

Surgery

7. Complete surgical resection (as outlined for stage I) is the usual practice and is the recommended standard of care.
8. For resection of thymoma, an open median sternotomy surgical approach is recommended.
9. Minimally invasive approaches (e.g., VATS) are not considered the standard of care and are not recommended at this time.

Radiotherapy

10. Routine adjuvant radiation is currently not recommended. Radiation should be considered in patients with high risk for local recurrence. These risk factors include invasion through the capsule, close surgical margins, World Health Organization (WHO) grade B type, and tumour adherent to pericardium.
11. Radiotherapy (RT) has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies and coronary heart disease. Possible risks and benefits need to be discussed with patients, particularly in younger individuals.

Systemic Therapy

12. Neither postoperative nor neoadjuvant systemic therapy is recommended for stage II disease.

Medically Inoperable Stage II Disease

13. Chemoradiation or radiation alone should be considered for patients who are medically unfit for surgery.

Stage III

14. Patients presenting with locally advanced or metastatic disease should be carefully evaluated for multimodality therapy that includes neoadjuvant chemotherapy, surgical resection or adjuvant postoperative chemoradiotherapy.

Resectable or Potentially Resectable Stage III Disease

Surgery

15. For stage IIIA, surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. In stage IIIB, patients should be assessed for surgery following neoadjuvant chemoradiotherapy.
16. If at thoracotomy complete resection is not found to be possible, maximal debulking (with appropriate vascular reconstruction) should be undertaken. Clips should be placed to mark residual tumour for adjuvant radiation. If it is apparent prior to surgery that complete resection may not be feasible, neoadjuvant chemoradiation should be considered prior to surgery.
17. Bilateral phrenic nerve resection is not recommended because of the severe respiratory morbidity that results.

Neoadjuvant Radiotherapy and Systemic Therapy

18. Neoadjuvant chemoradiotherapy is widely used in this setting.
    - The data supporting this standard is not yet established.

19. The optimal neoadjuvant therapy regimen for minimizing operative morbidity and mortality, and maximizing resectability and survival rates is not yet established.
    - Cisplatin-based combination chemotherapy regimens are recommended as reasonable options.

20. The optimal sequencing of radiotherapy and chemotherapy is not yet established.
    - If treatment volumes are small, concurrent chemoradiotherapy is recommended as a reasonable option.
    - If the initial tumour volume is considered to be too bulky, sequential therapy, with chemotherapy followed by radiation therapy, is recommended as a reasonable option. Resection may be performed prior to radiotherapy.

21. To establish the diagnosis of thymoma, either a computerized tomography (CT)-guided core-needle biopsy or an open surgical biopsy should be performed, prior to considering neoadjuvant therapy.

Adjuvant Radiotherapy and Systemic Therapy

22. Adjuvant radiotherapy is widely used in this setting and is recommended. Adjuvant chemotherapy may be a consideration.

Unresectable Stage III Disease

23. Where surgery is inappropriate, chemotherapy concurrent with, or sequential to, radiation therapy is recommended.
24. The definition of unresectable disease is debated, and may vary with surgical expertise, but is generally defined as extensive tumour involving middle mediastinal organs such as the trachea, great arteries, and/or heart that does not respond to cisplatin-based combination chemotherapy.

Stage IVA

25. The recommendations established for stage III disease are applicable to stage IVA cases as well. The following are notable modifications or exceptions to this:

Resectable or Potentially Resectable Stage IVA Disease

Surgery

26. Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. Surgery is recommended only if pleural and pericardial metastases can be resected.

Neoadjuvant Radiotherapy and Systemic Therapy

27. Neoadjuvant chemoradiotherapy is an option in this setting.
28. Cisplatin-based combination chemotherapy regimens are reasonable options.

Adjuvant Radiotherapy and Systemic Therapy

29. Adjuvant chemoradiotherapy is an option.

Unresectable Stage IVA Disease

30. Where surgery is not feasible because of extensive or technically unresectable pleural or pericardial metastases, chemotherapy is commonly provided. Chemotherapy concurrent with, or sequential to, radiation therapy is also an option.
31. In stage IVA, unresectable disease may include extensive bilateral and/or pleural-based disease, pericardial metastases, or extrathoracic metastases.

Stage IVB

32. These types of thymoma are extremely rare, and generic recommendations are not possible.

Surgery

33. Not applicable

Radiotherapy

34. Radiotherapy may be appropriate, particularly for life-threatening situations.

Systemic Therapy

35. Cisplatin-based combination chemotherapy is an appropriate option.
36. Octreotide, alone or in combination with a corticosteroid, may be a reasonable option for recurrent cases.

Recurrent Disease

Surgery

37. Surgical resection should be considered in patients with a localized recurrence after apparently successful initial therapy. In some patients with stage IV disease, the resection of isolated pleural metastases is an appropriate initial approach. For cases with multiple pleural metastases, chemotherapy, with or without subsequent surgery, is often appropriate.

Radiotherapy

38. Radiotherapy may be appropriate either alone or in combination with chemotherapy.

Systemic Therapy

39. Cisplatin-based chemotherapy may be an appropriate therapy either alone or as part of combined chemoradiotherapy.
40. Octreotide, alone or in combination with a corticosteroid, may be a reasonable option.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by a randomized controlled trial (RCT), three retrospective case reports, and one survey.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Increased survival and response to therapy
- Reduced risk of recurrence

POTENTIAL HARMS

Radiotherapy (RT) has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies and coronary heart disease.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Falkson C, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak D, Yu E, Smith CA, McNair S, Ung Y, Evans WK, Lung Disease Site Group. The management of thymoma: guideline recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2008 Sep 26. 41 p. (Evidence-based series; no. 7-11). [58 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Sep 26

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Lung Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Lung Disease Site Group (DSG) were asked to disclose potential conflict of interest information. No conflicts were reported.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

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Date Modified: 4/27/2009